M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 8, 1999

To: Dockets Management Branch (HFA-305)

From: Ted Sherwood
Management Analyst
Office of Generic Drugs

Subject: Presentation Regarding Human Generic Drugs to Docket 90S-0308

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Process Validation Update

Presented for: Arnold and Marie College of Pharmacy and Health Sciences

Date Presented: May 7, 1999

Presented by: Rashmikant M. Patel, Ph.D.

Number of Pages: 23

Ted Sherwood

Attachment

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90S-0308

M638

Arnold & Marie Schwartz College of Pharmacy and Health Sciences

Sixth International Symposium on Drug Development

May 7, 1999

Process Validation Update

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Process Validation Update

- Regulations
- References
- Memorandum of Understanding/ CDER-Field Agreement
  - Pre approval issues
  - Post approval issues
- Process validation
  - Drug substances
  - Drug Products
- Methods Validation
  - Examples
- Summary

Regulations

Current Good Manufacturing Practices Regulations (CGMPR)

21 CFR 211

Proposed Rule (CGMP)

61 FR 20104, May 3, 1996

New Drug Application Regulations (NDA)/Abbreviated New Drug Application Regulations (ANDA)

21 CFR 314.50(d)(1)(ii)(a)

21 CFR 314.94(a)(9)(i)

Chemistry Manufacturing and Controls (CMC)

Microbiology

Proposed Rule for CGMP (61 FR 20104, May 3, 1996)

Process validation
Validation protocol
Methods validation
Equipment suitability
Process suitability
Out-of-specification
Reprocessing
Manufacturing process
Blend uniformity testing, 21 CFR 211.110(d)

References

Sterile Drug Products Produced by Aseptic Processing (1987)

Process Validation Requirements for Drug Products Subject to Pre-market Approval (CPG 7132c.08)

Guide to Inspection of Oral Solid Dosage Forms Pre/Post Approval Issues for Development and Validation (Issued by ORA January 1994)

Bulk Pharmaceutical Chemical Inspection Guide (Revised September 1991)

General Principles of Process Validation (1987)

Blend Uniformity Analysis (PDA)

Blend Uniformity Analysis (Office of Generic Drugs draft Guidance)

OGD Policy and Procedure Guide # 4-89 on Microbiological Reviews (Revised 7/93)

Requesting Methods Validation for ANDAs (CDER MAPP 5221.1)

Validation of Analytical Methods (USP and ICH Guidelines Q2A and Q2B)

Memorandum of Understanding/CDER-Field Agreement

Roles and Responsibilities

. ORA field investigators
  Assure CGMP compliance
  Verify the authenticity and accuracy of the data

. CDER review scientists

  Review the sterile process validation package
  Evaluate test methods, data, and establish specifications

- Process validation is a field responsibility

- To be addressed post-approval

- CDER will not withhold approval of an application if

  Validation has not been attempted
  A validation protocol is not available
  Protocol is available, but does not adequately test all parameters

- CDER will concur with a withhold recommendation if

  Validation has been attempted
  Significant data integrity issues are documented
  Process cannot be validated
  Product fails to meet predetermined specifications
  A revised process has not been filed

Memorandum of Understanding/CDER-Field Agreement (October 14, 1994)

Pre-approval issues

Microbiological

Prospective Validation

Chemistry Manufacturing and Controls

Developmental Data (Validation Summary)

In-process controls (ANDA Section XXII)

Adequacy of Mixing and Homogeneity

Memorandum of Understanding /CDER-Field agreement (October 14, 1994)

Post-approval issues

Current Good Manufacturing Practice Regulations

Commitments filed in ANDA

Validation of Production Batches (Prospective Validation)

Formulation and Process Changes (e.g., SUPAC/ Revalidation)

Process Validation (Summary)

Drug Substance (Developmental or Prospective Validation)

Unit Operation .....Drying

Process Variables.....Time, Temperature, and Load

In-process Controls.....Residual Solvent

Example

Acceptance limits of N,N Dimethylformamide

Not an Organic Volatile Impurity

What was the question?

How was it justified ?

Process Validation (Summary)

Drug Products

Pre-approval data (summary)

Test batch or bio batch

Blend Uniformity Analysis

Historical Perspective

Inconsistency in the OGD Review Process

Chemistry Manufacturing and Controls Coordination Committee

Audit

Drug Product Technical Committee

Discussion with GPIA/NAPM/NPA

Draft Guidance for ANDAs

Product Quality Research Institute

Process Validation (Summary)

Drug Product (Tablets, Capsules)

Unit Operation.....Blending or mixing

Variables.....Time, speed, load

In-process control.....Blend Uniformity Analysis (BUA)

OGD Draft Guidance on Blend Uniformity Analysis

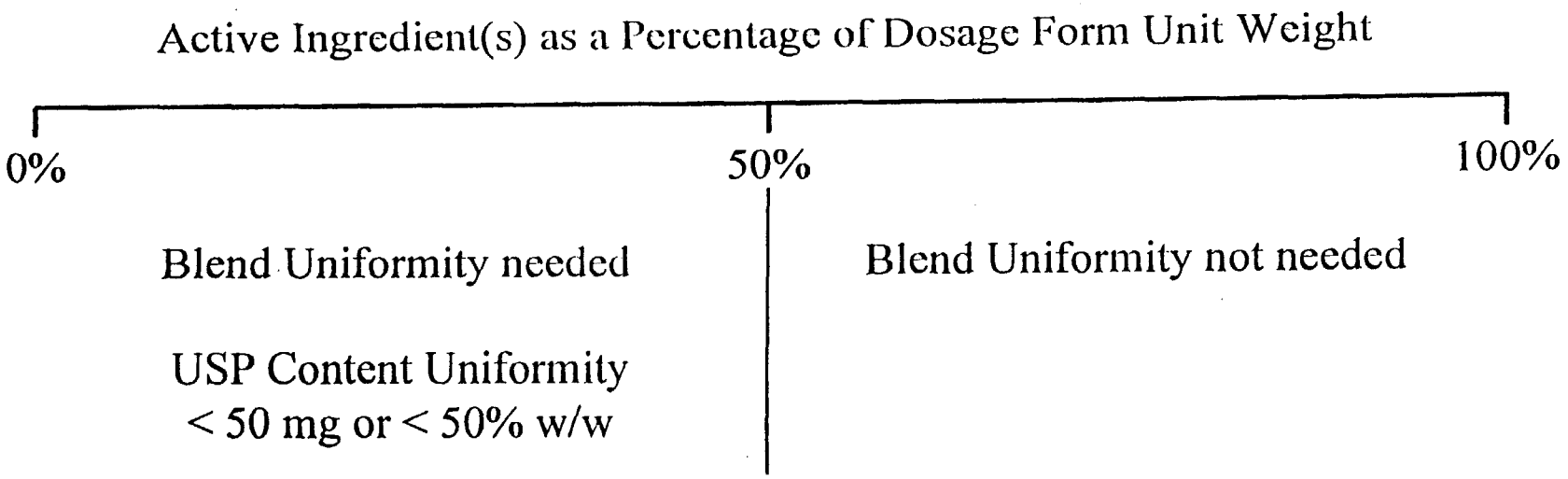
In-Process Controls

The analytical controls used during the various stages of manufacturing and processing of the dosage form should be fully described. Where feasible, the in-process specifications should be supported by appropriate data that may include, but should not be limited to, representative master/batch production and control records.

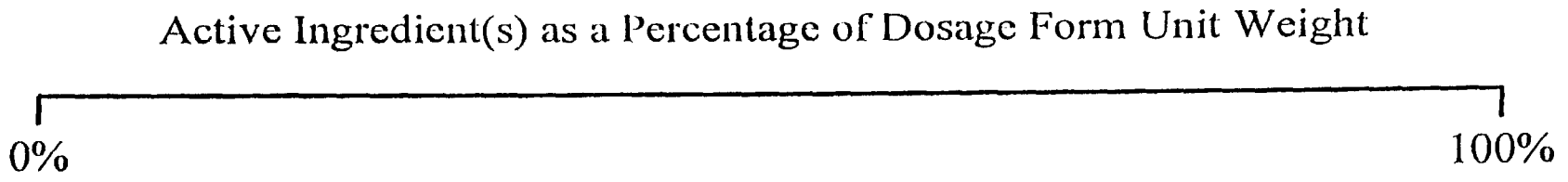
USP Content Uniformity Requirements

- If the drug product contains less than 50 mg of an active ingredient or if the drug product contains less than 50% w/w of an active ingredient in the dosage unit...

Blend Uniformity Analysis Proposed Guidance for Generic Drug Products



Blend Uniformity Analysis Proposed Guidance for Generic Drug Products



Complex Drug Products

Complex Processes

Consult Division Director

BLEND UNIFORMITY ANALYSIS

.Original application	Test batch
.Post approval	Major formulation/process change
.Production batches	CGMP
.Strengths and combinations	All
.Sampling	Blender or Drum
.Sample size	1 to 3x the drug product weight
.Sampling error	Probe/thief
.Number of samples	6 to 10
.Sample for analysis	Weight of a dosage form
.Acceptance criteria (Proposed)	Report individual values Mean: 90 to 110% % RSD: Less than or equal to 5

Methods Validation

Requesting Methods Validation for ANDAs (MAPP 5221.1)

Process

Methods Verification

Methods Validation Process

Examples

METHODS VERIFICATION

Applies to official (USP) drug products

Email notification to laboratory upon filing

Laboratory obtains sample by mail. Tests using official USP methods.

Optional program

OGD does not seek nor await results before action (NA or AP)

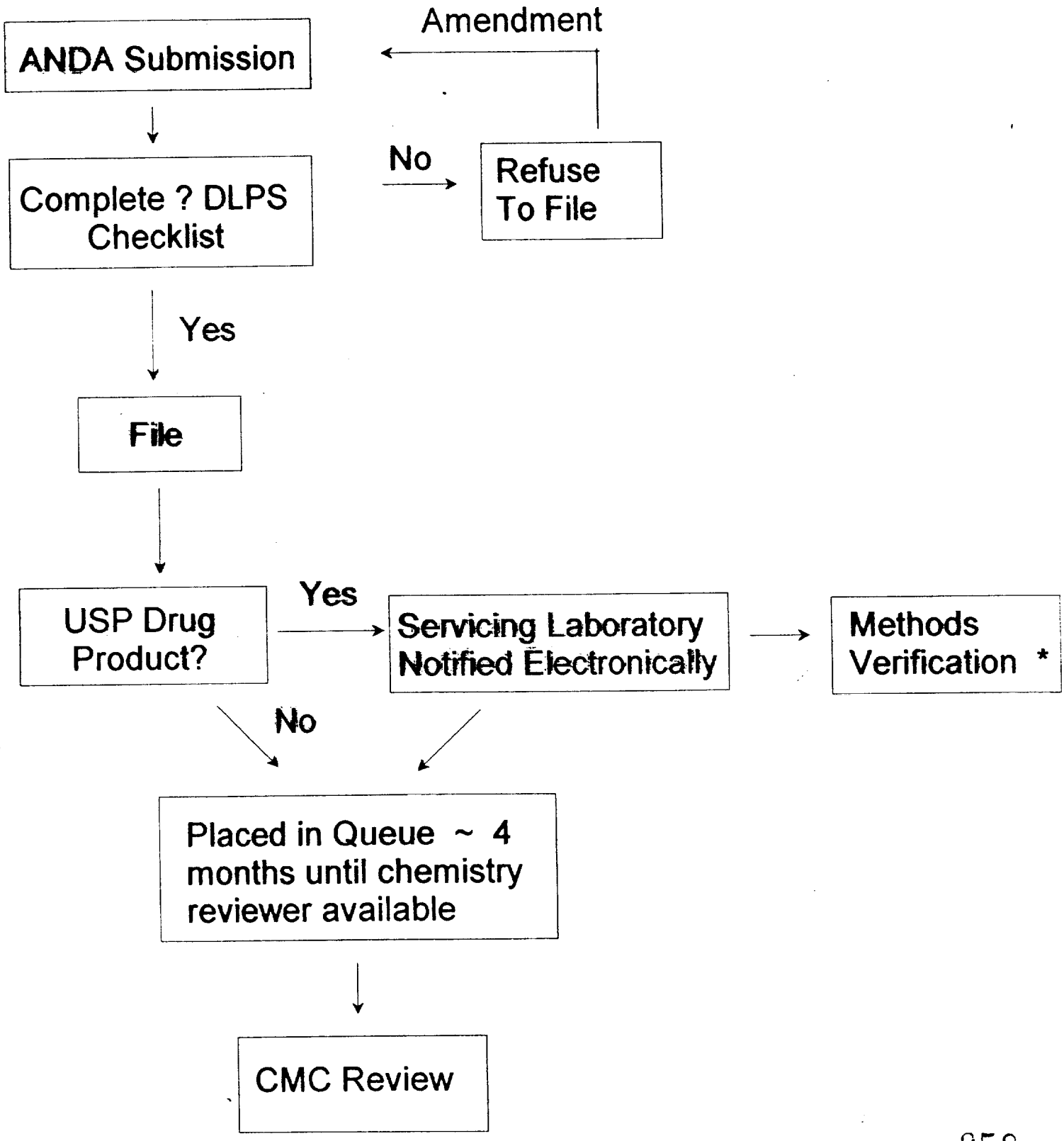
OGD will consider adverse results, if available

Alternate methods for compendial attributes not tested in laboratory

Additional methods for non-compendial attributes not tested in laboratory

CDER/ORA Ad Hoc group likely to recommend deletion of this program. Requires Field/Drug Committee concurrence.

ANDA Methods Validation Process



30-Day Wait

Applies when all aspects of ANDA are acceptable to Team Leaders except pending methods validation (MV)

Post approval MV commitment obtained from applicant

Lab notified by Project Manager (PM) at start of 30 day clock

Lab contacted by PM at end of 30 day clock

OGD will approve at this point unless:

Applicant delayed sample submission

Adverse information is available about Method Validation program in process

DRUG PRODUCT TECHNICAL COMMITTEE MEMBERS

- Office of Generic Drugs

  Dave Gill
  Upinder Atwal
  Andrea High

- Office of New Drug Chemistry

  Martha Heimann
  Raj Uppoor
  Amit Mitra
  Joseph Sieczkowski

- Office of Compliance

  Luann Pallas

- Office of Testing and Research

  Ajaz Hussain

Summary

Process validation

Field/Microbiologist

OGD

BUA, Methods validation